11. (Twice Amended) A composition for the treatment of skin wounds, said composition comprising a ribosome-depleted mixture of the bone morphogenetic proteins BMP-3 and TGF-β2, said mixture of proteins having been treated to remove ribosomal proteins, said composition including a pharmaceutically acceptable carrier.

13. (Twice Amended) A composition for the treatment of skin wounds, said composition comprising a mixture of proteins comprising BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, TGF-β1, TGF-β2, TGF-β3, and FGF-1 in a pharmaceutically acceptable carrier.

18. (Twice Amended) A method of promoting the healing of a skin wound, said method comprising applying a composition of claim 13 to a skin wound.

25. (Amended) A method of promoting the healing of a skin wound comprising applying to said skin wound a composition comprising a mixture of the bone morphogenetic proteins BMP-2, BMP-3, BMP-6, and TGF-β2 in a pharmaceutically acceptable carrier.

REMARKS

In the present Office Action, claims 1-26 have been considered. Claim 22 has been withdrawn pursuant to a restriction requirement. The Examiner has (1) rejected claims 1-5 under 35 U.S.C. § 102(b) over U.S. 5,393,739 to Bentz et al. ("Bentz"); (2) rejected claims 1-8 under 35 U.S.C. § 102(b) over U.S. 5,459,047 and 5,543,394 to Wozney et al. ("Wozney '047" and "Wozney '394"); (3) rejected claims 9-12 under 35 U.S.C. § 102(b) over U.S. 5,290,763 to Poser et al. ("Poser '763"), US 5,563,124 to Damien et al. ("Damien"), and U.S. 5,371,191 to Poser et al. ("Poser '191); (4) rejected claims 1-8 under 35 U.S.C. § 102(e) over U.S. 6,150,328 to Wang et al. ("Wang"); (5) rejected claims 13-18, 20 and 23 under 35 U.S.C. § 103(a) over Wang in view of Bentz and U.S. 4,950,483 to Ksander et al. ("Ksander"); (6) rejected claims 19 and 21 under 35 U.S.C. § 103(a) over Wang, Bentz and Ksander in view of US 6,124,273 to Drohan et al. ("Drohan"); (7) rejected claim 24 under 35 U.S.C. § 103(a) over Wang, Bentz, and Ksander in view of U.S. 5,616,490 to Sullivan et al. ("Sullivan"). Claim 26 has been allowed.

In the present Amendment, claims 1, 9, 11, 13, 18, and 25 have been amended. No claims have been canceled or added, and no new matter has been introduced. Claims 1-21 and 23-25 remain for consideration.

I. Rejections under 35 U.S.C. § 102(b)

Claims 1-5 stand rejected under 35 U.S.C. §102(b) as anticipated by US 5,393,739 to Bentz et al. (hereinafter "Bentz"). The Examiner has maintained that the prior art use of bone morphogenetic proteins (BMPs) and other polypeptides for treatment of bone fractures (and other osteogenic uses) constitutes wound healing within the meaning of the claims. Applicants have amended independent claims 1, 9, 11, 13, 25 and 26 to more particularly indicate that the wounds to be treated by the methods and compositions of the present invention are **skin wounds**. Support for these amendments stems directly from Examples 1, 2 and 3 in the specification, which disclose the treatment of full thickness skin wounds in nude mice at page 9 line 15 – page 14 line 9. In addition, Applicants have pointed out in the Amendment filed May 13, 2002 that the term "wound healing" as used in the present application is distinct from osteogenesis. See, e.g., Specification at page 5, lines 32-33.

Applicants disagree that osteogenic uses of BMPs (which are the only uses disclosed in Bentz) constitute wound healing as used in the present application. However, even applying the Examiner's view of the term, none of the cited references teaches or suggests the use of BMPs in healing **skin wounds**, as presently recited in all of the independent claims. Accordingly, it is respectfully submitted that the amendments overcome the cited art and that the claims are allowable.

Neither Bentz nor any of the other prior art references disclose any actual results showing the use of BMPs for the treatment of skin wounds. Moreover, of the art cited, only US 4,950,483 to Ksander et al. (hereinafter "Ksander") explicitly deals with skin wound treatment at all, and that reference only discloses treatment with 1) **TGF-β2** alone (Example 6) and 2) **TGF-β2** in combination with **aFGF** (Example 9). There is **no** disclosure whatsoever in Ksander of the use of BMPs to treat skin wounds. Indeed, it is conspicuous that even the suggestion of **other proteins** which ***might*** be useful in treating skin wounds omits BMPs altogether. Ksander at col. 2 lines 7-10 (disclosing EGF, PDGF, aFGF, bFGF, CTAP, and TGFs and ***not*** disclosing BMPs). Accordingly, Applicant respectfully submits that to the extent it is relevant at all, Ksander

teaches away from the claimed invention. None of the remaining references remedy any of the serious deficiencies of Ksander.

Claims 1-8 stand rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. Wozney '047 and Wozney '394. Claim 1 has been amended to recite a method of promoting the healing of a **skin wound**. It is respectfully submitted that Wozney '047 and Wozney '394 do not disclose any operative embodiment for treating skin wounds with BMPs. The mere suggestion that the compositions "may also be used for wound healing and tissue repair," Wozney '047 at col. 2 lines 47-49, is not an affirmative teaching of healing a skin wound, **especially** in view of the Examiner's position that bone fracture repair is a species of wound healing. At most, the Wozney '047 language is a suggestion that it may be "obvious to try" to use the compositions for wound healing. The Federal Circuit has repeatedly rejected the "obvious to try" standard as a sufficient basis for an obviousness rejection, much less a rejection for anticipation.

Outcomes in the biological arts are notoriously difficult to predict, and given the complete absence of any enabling disclosure for treating skin wounds in the Wozney '047 and '394 references, neither reference can be said to provide an enabling disclosure for treating a skin wound. Although the '047 and '394 patents suggest that BMP-5, BMP-6, and mixtures of BMP proteins, **may** be useful for wound healing, there is no example or specific teaching that those proteins are **actually** capable of promoting effective angiogenesis, efficient collagen deposition and proper epithelialization to heal or close a **skin** wound. In Applicants' Specification (e.g., at page 2, line 27 through page 4, line 26; and at page 11, lines 5-8) the unpredictability of this field (i.e., promotion of wound healing) is illustrated by summaries of previous test results with a variety of growth factors. For at least these reasons, Applicants submit that claims 1-8 as amended distinguish over Wozney '047 and '394.

Claims 9-12 further stand rejected under 35 U.S.C. § 102(b) as anticipated by Poser '763, Damien, and Poser '091. It is respectfully submitted that the osteogenesis studies disclosed in Poser '763, Damien, and Poser '091 (which are co-owned with the instant application) fail to teach or even suggest the use of such compositions for treating skin wounds. Moreover, the Poser and Damien patents do not teach modification of that original protein mixture as described in claims 9-12 (i.e., to remove histones, or ribosomes or to ensure that the proteins are phosphorylated or glycosylated). For at least these reasons, claims 9-12 are allowable over the Poser '763, Damien, and Poser '091 patents.

Claims 1-8 further stand rejected under 35 U.S.C. § 102(b) as anticipated by Wang. Nothing in Wang suggests the use of BMPs in compositions for treating **skin wounds**. A word search of the Wang patent reveals that it fails to even mention the word "skin" at all. Instead, its focus is the treatment of bone and cartilage defects, which are not implicated by the claims as amended. Accordingly, Wang cannot anticipate claims 1-8, and Applicants respectfully request that the rejected be withdrawn.

II. Rejections under 35 U.S.C. § 103

Claims 13-18, 20 and 23 stand rejected under 35 U.S.C. § 103(a) as obvious over Wang in view of Bentz and Ksander. As stated above, Wang only fails to even mention skin wounds, and is directed instead to bone and cartilage defects. Bentz likewise does not suggest treatment of skin wounds. Ksander teaches away from the use of BMPs to treat skin wounds. Accordingly, none of the references, either alone or in combination, can be used to achieve the claimed inventions.

More specifically, Ksander suggests numerous proteins may possibly be used for treating skin wounds, but specifically omits BMPs as potential candidates for treating skin wounds. Bentz teaches bone growth compositions containing certain BMP proteins, TGF-β1 and/or TGF-β2, but there is no demonstration or suggestion of any treatment compositions for skin wounds. Since tissue repair or wound healing is a complex process with quite different considerations from those related to osteogenesis (see, e.g., Applicants' Specification at page 2, lines 3-13), one of skill in the art would not be motivated to combine these references as proposed by the Examiner. Indeed, the absence of BMPs from Ksander would teach away from such a combination. However, even if one were to combine the references, there is no teaching or suggestion of which of the many proteins described should be combined to obtain a composition for treating skin wounds. Further, nothing in any of the references would provide guidance to persons of skill in the art as to which of the many possible combinations of proteins would provide a reasonable expectation of success in treating skin wounds.

Without the teachings of the present disclosure, the present combinations of proteins simply cannot be arrived at as a composition for treating skin wounds. Such hindsight reconstruction is impermissible, and Applicants respectfully submit that the claims are allowable.

Claims 19 and 21 stand rejected under 35 U.S.C. § 103(a) as obvious over claims 19 and 21 under 35 U.S.C. § 103(a) over Wang, Bentz and Ksander in view of Drohan. Drohan fails to remedy the deficiencies noted above with respect to Wang, Bentz and Ksander. Accordingly, its addition to the foregoing references fails to render the claimed inventions obvious over the combined art.

Claim 24 stands rejected under 35 U.S.C. § 103(a) as obvious over Wang, Bentz, and Ksander in view of Sullivan. Sullivan involves compositions for treating skin diseases (such as psoriasis) but like Ksander fails even to mention bone morphogenetic proteins (BMPs), much less suggest their use with other proteins for treating skin wounds. Accordingly, the combined references fail to render the claimed inventions obvious.

IV. Conclusion

The Examiner has indicated that claim 26 is allowable. In view of the foregoing amendments and remarks, it is respectfully submitted that the remaining claims as amended are allowable over the prior art of record. Accordingly, it is requested that the proposed Amendment be entered and that a Notice of Allowance be issued.

Respectfully submitted,

February 13, 2003
Date

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APPENDIX A

CLAIMS MARKED-UP TO SHOW CHANGES MADE

1. (Twice Amended) A method of promoting [wound] the healing of a skin wound comprising applying to said skin wound a composition comprising the growth factors BMP-3 and TGF-β2 in a pharmaceutically acceptable carrier.

9. (Twice Amended) A composition for the treatment of skin wounds, said composition comprising a histone-depleted mixture of the bone morphogenetic proteins BMP-3 and TGF-β2 [comprising a bone-derived protein cocktail which, when subjected to sodium dodecyl sulfate polyacrylaminde gel electrophoresis, yields a reduced or non-reduced protein band profile as indicated in Figure 1], said [bone-derived protein cocktail] mixture of proteins having been treated to remove histone proteins, said composition including a pharmaceutically acceptable carrier.

11. (Twice Amended) A composition for the treatment of skin wounds, said composition comprising a ribosome-depleted mixture of [proteins comprising a bone-derived protein cocktail which when subjected to sodium dodecyl sulfate polyacrylaminde gel electrophoresis, yields a reduced or non-reduced protein band profile as indicated in Figure 1] the bone morphogenetic proteins BMP-3 and TGF-β2, said [bone-derived protein cocktail] mixture of proteins having been treated to remove ribosomal proteins, said composition including a pharmaceutically acceptable carrier.

13. (Twice Amended) A composition for the treatment of skin wounds, said composition comprising a mixture of proteins comprising BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, TGF-β1, TGF-β2, TGF-β3, and FGF-1 in a pharmaceutically acceptable carrier.

18. (Twice Amended) A method of promoting the healing of a skin wound [healing], said method comprising applying a composition of [as in] claim 13 to a skin wound.

25. (New) A method of promoting the healing of a skin wound [closure] comprising applying to said skin wound a composition comprising a [bone-derived] mixture of [phosphorylated and glycosylated] the bone morphogenetic proteins BMP-2, BMP-3, BMP-6, and TGF-β2 in [which, when subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis, yields a reduced or non-reduced protein band pattern as identified in Figure 1, from which protein mixture ribosomal proteins and/or histone proteins have been removed, said composition including] a pharmaceutically acceptable carrier.

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